EXHIBIT 1

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THE WITNESS: So statistical power depends on the expected degree of difference between two groups and the expected variability, and since those things aren't known, you have to first start by interrogating the data you have and then see if that can predict for you what kind of power that you need.

So when you're saying it wasn't powered, nobody has any idea what the expected frequency of this condition is. So there would be no way to a priori power the study.

BY MR. SLATER:

Q. Do you know what Daiichi's position is on whether or not this ROADMAP study is adequately powered to answer the question of whether or not olmesartan causes gastrointestinal side effects?

A. I do not.

Q. If the study is not adequately powered to answer that question, it would be unscientific to rely on the study data to answer the question; right?

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MR. CHRISTIAN: Objection. Form.

THE WITNESS: That's a verbatim question you just asked me, and I just said to -- I can't determine whether it's properly powered because we don't know what the expected frequency in the population of this is.

You would have to know that in order to make an a priori estimation of what power should be.

BY MR. SLATER:

Q. Doctor, I'm not asking you if it's adequately powered or not. We already know you can't tell me that.

My question is: Assuming it is not adequately powered -- I'm going to rephrase.

Assuming the ROADMAP study is not adequately powered to give data that would be useful regarding the frequency of gastrointestinal side effects due to olmesartan, you would not want to rely on it and it would be unscientific to do so to answer the question of causation; correct?

MR. CHRISTIAN: Objection. Form.

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THE WITNESS: Well, I think that this is a useful document here in that it gives us some sense of what the expected event rates are, and now we have an idea. But unfortunately for your case, there's no difference between the placebo and the olmesartan.

So, you know, the onus is not to prove that there's not an association.

BY MR. SLATER:

Q. Move to strike.

Do I understand you correctly to be saying the usefulness of the ROADMAP study is it shows that, to the extent that olmesartan-associated enteropathy exists, it's rare or uncommon? Is that -- is that basically what you're saying?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: No. I'm saying that what the ROADMAP study would argue is that it doesn't exist.

BY MR. SLATER:

Q. Well, you can't get that information from the ROADMAP study if it's

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underpowered to answer that question; right?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: So what evidence do you have that it's properly powered or underpowered?

BY MR. SLATER:

Q. Hey, Doctor, you don't have an opinion whether it's powered adequately or not; right?

A. That's true. All I can say is it's an observation that might now provide guidelines to now do a power analysis for the next study.

Q. Move to strike after "that's true."

You've already established nobody would ever do such a study to -- to look at gastrointestinal side effects because you already told us it would take too many people and take too long. Didn't you tell me that earlier?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: Well, I think that if that was the only purpose of the study, that might be true, but I do

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realize now that there could be opportunities if there were other studies being done with olmesartan to look at similar phenomenon as what was done in the ROADMAP.

Now with this in mind, I think there could be a subcomponent of the study where they could monitor the GI side effects and potentially construct a power analysis based on these data here.

BY MR. SLATER:

Q. You haven't done that analysis or constructed any such study; right?

A. No.

Q. And it's speculation as you sit here now that you're talking about. You're speculating that something like that could be done; right?

A. I suppose, but it would be -- it would be an attractive idea to get more insight into this situation.

MR. CHRISTIAN: Could we take a quick bathroom break, Adam?

MR. SLATER: Just one more

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question.

BY MR. SLATER:

Q. Doctor, I think you looked at the letter to the editor by Menne and Haller while you were trying to answer my question before?

A. Yes.

Q. Correct?

A. Yeah.

Q. Despite everything they said in their letter, they said they can't rule out the possibility of an association basically; right?

A. (Reviewing document).

They say they can't rule out that this could be a very rare situation where it could play a role, but their data do not identify a link. That's what their conclusion is.

Q. And they actually said just above that that they didn't observe an intestinal effect of olmesartan, but they said this finding might be because sprue-like enteropathy is a rare event; right?

They actually acknowledge the possibility that the study was underpowered to show this; right?

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A. Can you tell me where that was?

Q. Sure. Right-hand column first page, last paragraph.

"This finding might be because sprue-like enteropathy is a rare event."

A. Right. Yeah, I see they say that.

MR. SLATER: All right. You want to take a break?

MR. CHRISTIAN: Yeah.

THE VIDEOGRAPHER: Time now is 2:20. We are going off the record. This is the end of Disk No. 3.

(A brief recess was taken.)

(Document marked for identification purposes as Gutman Exhibit 14.)

THE VIDEOGRAPHER: The time now is 4:40 -- excuse me -- 2:41. We're back on the record. This is the beginning of Disk No. 4.

BY MR. SLATER:

Q. Doctor, I have given you Exhibit 14, which is an article from Marthey et al.

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"Olmesartan-associated enteropathy: result of a national survey."

Are you familiar with that study?

A. Yes.

Q. Now, in this study, they point out in part that when the patients were diagnosed when they were actually under treatment, olmesartan was not known as a potential cause of enteropathy. Therefore, most patients were treated as if they had an autoimmune enteropathy; correct?

A. You'll have to point -- it's -- I don't remember that exactly. Can you point out where they say that?

Q. On page 1105 under Outcome First paragraph.

A. Okay.

Q. So these doctors who were treating these patients didn't have the benefit of knowing that olmesartan was one of the potential causes for what they were seeing; correct?

A. Correct.

Q. Now, if you look at page 1106,

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there were patients who were stopped on olmesartan and it says 9 out of 10 had clinical remission. That's in the first carryover paragraph by the left column.

A. Right.

Q. When olmesartan was reintroduced, all had clinical relapses; correct?

A. Yeah. Yes. They said that it was reintroduced to 9, yes.

Q. That fact that 9 out of 9 had positive rechallenge -- rechallenges is evidence supporting a finding of causality; correct?

A. Well, as we've said before, this was not any sort of controlled protocol. It's just a retrospective description of a story.

Q. Just out of curiosity, you're sure there's no protocol for this study?

A. Well, the methods just says:

"We contacted by e-mail investigators to report their observations."

So I'm not seeing anything here about a unified protocol.

Q. Okay. On page 1107 is the discussion and they say in the first paragraph in part:

"Olmesartan is likely to be causal as interruptions were followed by clinical remissions and reintroductions were followed by relapses."

Do you see that statement?

A. Yes.

Q. From a clinical perspective, that's a reasonable medical judgment; correct?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: You could argue that in these 9 patients that there was some suggestion that they had a reaction to olmesartan that was specific to them, and when they were restarted, there was a relapse. That's what they've stated here, but, again, it's not really under any specific protocol.

BY MR. SLATER:

Q. You discount this data because there wasn't a protocol and because it wasn't a controlled study; is that correct?

A. Well, in my report, I called it "Level IV evidence." So I don't throw it out completely. I just say it's -- it's not the higher level evidence.

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Q. You're not opining that these 9 patients didn't get better -- well, rephrase. Let me ask it differently.

Is it your opinion that these 9 patients who are described here didn't really get better when they got off the drug and didn't really get sick again when they went back on olmesartan?

A. I can't really say for sure because it's not the same thing. It's as a controlled study. In other words, they just accepted information from various GI docs in the country. So it's not the same thing as a well-defined follow-up.

Q. Who would have a motivation to do the sort of controlled study that you're suggesting would need to be done in order to prospectively evaluate olmesartan-associated enteropathy? Who would actually have an incentive to do that study and to spend that money?

MR. CHRISTIAN: Objection. Form.

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THE WITNESS: Right. I don't disagree with you.

But what I'm saying is that, as we were just talking about in the ROADMAP study, if you have a lot of patients that you're tracking very carefully, like I used the example of the Framingham Heart Study or the Nurses Health Study, there's much more opportunity to interrogate that data in a systematic way rather than just receiving cases that come into you via community practice doctors.

BY MR. SLATER:

Q. Move to strike after the "right." I think he said something to the effect of "right, I don't -- I agree with you," or whatever he said. I don't have the exact language but moving to strike the last part of the answer.

In terms of evaluating olmesartan-associated enteropathy, sprue-like enteropathy, whatever you want to call it, the evidence of dechallenges and rechallenges has to be looked at as an important component of the analysis; correct?

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A. If they were properly done, but we've been down this road before in this deposition where I've said that I don't think that these case reports constitute what I would consider a proper challenge and rechallenge.

Q. Are there any dechallenges or rechallenges that you feel are of a sufficient level of scientific evidence that you actually think that they are of significance that you've seen any article or study you've seen?

A. Well, I'm thinking about things like clinically. There are children that have severe food allergies, and they see experts in this. And then what happens is their life is really turned upside down by the fear that they're going to have anaphylactic shock if they're in the room with somebody that's eating peanuts or what have you, and there are physicians that specialize in slowly and meticulously re-challenging those children to determine what foods they can be around and what foods they can eat.

That's just a clinical example of how there are people with a lot of experience

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have study protocols for taking care of patients with complex issues like that.

Here we're just dealing with kind of retrospective observations. These are observational studies.

Q. Okay. Move to strike.

MR. CHRISTIAN: Did you finish your answer?

THE WITNESS: The last thing I would say is just these are -- these are observational studies.

BY MR. SLATER:

Q. Move to strike.

My question is this: Are there any documented dechallenges or rechallenges in any of the articles that you're relying on for your opinions that you consider to be valid scientifically?

A. I don't believe there are any, no.

Q. Since in forming your opinions you have put aside all of the reports of dechallenges and rechallenges as not being of any real significance to you.

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Do I understand that?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: You know, as I've been trying to say here, I'm not taking articles that people did their best to write and just saying, I'm not going to read it or I'm not going to consider it.

I'm saying that I'm going to grade the level of evidence, and I just feel like the level of evidence with these challenge, rechallenge, as you call it, is -- is low.

I'm not saying that I didn't read it or consider it or that it can't be considered at all or debated. I'm just saying that it's -- the quality of the evidence is low.

BY MR. SLATER:

Q. For the 9 patients who had positive dechallenges and positive rechallenges, as described in Marthey, olmesartan is the likely cause of their clinical symptoms; correct?

MR. CHRISTIAN: Objection. Form.

BY MR. SLATER:

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Q. Based on the information available in this article?

MR. CHRISTIAN: Same objection.

THE WITNESS: I'm not sure I see the word "rechallenge" or "dechallenge" anywhere in this article, first of all.

BY MR. SLATER:

Q. No. I'm using the word "rechallenge" and "dechallenge." But this talks about the fact on page 1106:

"Olmesartan interruptions were followed by clinical remissions in 9 of 10 cases. Olmesartan reintroductions were followed by clinical relapses in 9 of 9 cases."

So with regard to those 9 patients, the likely cause of their condition was the olmesartan; correct?

A. So --

MR. CHRISTIAN: Objection. Form.

THE WITNESS: -- one of the confounding variables in the study that's really problematic is a lot of these patients were on steroids.

So I don't know how well it's

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delineated here whether the people -- so let's imagine somebody gets better on steroids, which controverts the Mayo Clinic study, which we previously discussed, where they indicated in that study that 20 of the 22 patients had failed to respond to steroids.

Now we have this study where they say that the majority of the patients received steroids. So what could easily have happened is that they might have gone off -- they might have gotten better on steroids.

Steroids could be treating something, autoimmune enteritis or some form of inflammation caused by another factor. They get better and then over time maybe they were going to get worse again anyway if they didn't get put back on steroids.

I really don't know. Like Crohn's disease or anything like that, and it just could be that they were looking well and then they stopped the

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steroids.

We see all the time in patients with -- with colitis that -- ulcerative colitis or Crohn's that they get off the steroids and then they get well and they come off the steroids, they get sick again. So there could be confounding variables.

BY MR. SLATER:

Q. Well, looking at the summary on the abstract on the start of the article. At the bottom of the results, it says:

"29 patients were in remission since olmesartan interruption including 26 without immunosuppressants."

You see what I just read?

A. Yes.

Q. For those 26 patients at least, would you agree that the likely cause was the olmesartan?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: I mean, it's possible. I don't know that I'm willing to say likely because, again, this is

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just sort of another case series.

BY MR. SLATER:

Q. From a clinical perspective with the information that's here, it would be reasonable clinical judgment by the doctors treating those patients to determine that those 26 patients, the cause of their condition was olmesartan.

That would be a reasonable clinical judgment in the course of treating that patient; correct?

A. I think that if they properly ruled out much more common causes of the syndrome of these types of conditions, then I think that in the individual cases if a treating physician feels that it's best to stop the olmesartan, I don't have a problem with that.

Q. The reason to stop the olmesartan and actually not to put the patient back on it because they already got better when they were off it, the reason the doctor would be doing that is because they believe the olmesartan was causing the condition, so I don't want to put the patient back on the drug.

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That would be a reasonable clinical judgment; right?

A. I would say right, except for the fact that this is a very short paper, and I really don't know what the treating physicians were thinking. There's no -- there's no information here about what the thought process was of the treating physicians.

Q. Move to strike from "except" forward.

I'm asking this: With regard to the 26 patients who got off of olmesartan, got better and they weren't taking immunosuppressants, if those doctors said, I'm not putting you back on olmesartan, I think because of the dechallenge olmesartan was probably causing your condition so you shouldn't take it anymore, that would be a reasonable clinical judgment; right?

A. I would say for those individuals that that would be a reasonable judgment.

MR. SLATER: Laura, let's go to document 4 and mark that as the next exhibit.

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THE REPORTER: Exhibit 15.
(Document marked for identification purposes as Gutman Exhibit 15.)
BY MR. SLATER:
Q. All right. Doctor, I've handed you a case report and review of the literature. The first author's last name is Kulai, K-u-l-a-i.
Do you see that?
A. Yes.
Q. And this -- this case report, if you look on the case presentation -- I'm not going to read the whole thing out loud, but if you go through it and you just read along with me, he had a 5-week history of non-bloody diarrhea, vomiting, and 20-pound weight loss.
Do you see that right in the beginning?
Do you see that, Doctor?
A. Oh, yeah. Sorry. Right at the beginning. Okay.
Q. And those symptoms are consistent with the syndrome of olmesartan-associated enteropathy, sprue-like enteropathy described

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throughout the literature; correct?
A. They're consistent with, but they could also be consistent with other things.
Q. Move to strike from "but" forward.
There's then a history that's given about an issue with his eye, and then they go through that he had no fevers, no joint pain, no skin changes, no recent travel, a past medical history, including kidney stones, hypertension, aortic valve replacement.
They go through his medications including olmesartan, hydrochlorothiazide, which is Benicar HCT. His other medications including ASA, vitamin C, a multivitamin, cod liver, acetaminophen.
Do you see all that?
A. Yes.
Q. Then they go through his blood workup. He had an acute kidney injury, presumably secondary to dehydration.
Do you see that?
A. Yes.
Q. He had normocytic anemia. They

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go through his albumen, his electrolytes, etc. Nonanion gap metabolic acidosis.
You see all that?
A. Yes.
Q. Negative for culturing, parasites, C diff. All that was negative, and then it shows that his testing for tTG antibodies negative also; correct?
A. Right.
Q. Biopsy showed marked villous blunting and near complete villous atrophy of the small intestinal mucosa. Increase in intraepithelial lymphocytes, neutrophils. It talks about the crypts.
It gives what the histopathology was; correct?
A. Right.
Q. It talks about the workup in the hospital and the fact that he was negative for syphilis, Lyme's disease, sarcoid, tuberculosis.
All that was negative?
A. Right.
Q. Right?
A. Yeah.

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Q. Then it shows that his diarrhea resolved within two weeks of olmesartan discontinuation, his anemia improved to baseline, and he returned to his previous weight within three months, and then 14 weeks later he had complete resolution of the villous atrophy and inflammatory changes.
Do you see all that?
A. Yes.
Q. If you look at that entire picture as described, the likely cause of this person's condition would be the olmesartan; correct?
A. Well, on face value, you might think that, but I do find this description of the uveitis to be worrisome because uveitis is a classic extraintestinal manifestation of Crohn's disease.
Q. For what?
A. For Crohn's disease, which is another disease.
Q. Would getting off of olmesartan result in resolution of symptoms of Crohn's disease if it was Crohn's disease?

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A. No, I'm not saying that.
I'm just saying that it's an odd scenario here that maybe this patient has some other sort of autoimmune disorder going on. I can't dispute the fact that as written here that the patient appears to have gotten better after the olmesartan, but uveitis is, you know, not something that's at all been associated with this syndrome and it seems to be concomitant with his situation. So would actually make me think about some sort of autoimmune situation.
Q. If this patient had an unrelated autoimmune situation, you would not expect that getting off of olmesartan would resolve the histopathology and the symptoms as described here; correct?
MR. CHRISTIAN: Objection. Form.
THE WITNESS: I don't dispute that. I'm just saying that it could be a coincidence. I agree that it would be a bit of an unusual coincidence, but I don't believe that, you know, getting off the olmesartan should affect the eye, but somehow his eye improved.

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I didn't -- I don't quite know whether they're trying to state that the olmesartan affected his eye.
BY MR. SLATER:
Q. Move to strike after "I don't dispute that."
If his condition was caused by something other than the olmesartan -- I'm talking about his gastrointestinal condition -- they would not be able to say what they say on the bottom right corner of page 2, that last paragraph where it says:
"The case described here demonstrated full symptomatic and pathologic resolution after suspension of olmesartan within a 4-month period."
You wouldn't expect them to be able to say that if this gastrointestinal syndrome was due to something other than the olmesartan; correct?
MR. CHRISTIAN: Objection. Form.
THE WITNESS: I mean, as I said, it could be a coincidence, and it's only one patient we're talking about here.

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BY MR. SLATER:
Q. To a reasonable degree of medical certainty, the fact that the patient had full symptomatic and pathologic resolution after suspension of olmesartan within a 4-month period leads to the opinion that olmesartan was the likely cause to a reasonable degree of medical certainty; correct?
MR. CHRISTIAN: Objection. Form.
THE WITNESS: You know, I would love to see a higher powered view of that Figure 2. I'm not convinced that that biopsy is normalized. I mean, yeah, the villi are back, but it looks like to me like there's lamina propria expansion still. So it doesn't look completely normal to me.
BY MR. SLATER:
Q. Move to strike.
Based upon the fact that there was full symptomatic and pathologic resolution after suspension of olmesartan, including the symptoms of non-bloody diarrhea, vomiting, and a 20-pound weight loss, and histopathology as

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described, to a reasonable degree of medical certainty the likely cause of that gastrointestinal syndrome is the olmesartan in this patient. That's the likely cause; correct?
MR. CHRISTIAN: Objection. Form.
THE WITNESS: Well, I just stated that I don't know that I accept the idea that the histopathologic resolution was complete, which you just stated the authors said, but to my look at this figure I'm not convinced that it's resolved.
BY MR. SLATER:
Q. Are you holding yourself out as an expert in the field of histopathology and the reading of slides?
A. I think that I -- although I'm not a board-certified pathologist, most of my papers have histopathology in them, and I consult multiple times a week with our two different research pathologists that I work with in all my projects. So I have a high level of understanding of histopathology.
Q. As between the biopsy images in

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Figure 1 versus Figure 2, do you agree that there is significant improvement in the histopathology?
A. Yes.
Q. So taking together the significant improvement in the histopathology at 14 weeks, the resolution of the clinical symptoms of non-bloody diarrhea, vomiting, and a 20-pound weight loss after the patient stopped taking the olmesartan, the likely cause of the gastrointestinal syndrome is olmesartan.
That's the likely cause; correct?
MR. CHRISTIAN: Objection. Form.
THE WITNESS: It is a potential cause, yes.
BY MR. SLATER:
Q. Likely cause; right?
A. Say it again.
Q. Likely cause; correct?
MR. CHRISTIAN: You have to try one more time, Adam. We didn't hear that one at all.
BY MR. SLATER:
Q. Okay. That is the likely cause; correct?

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A. I mean, with the same degree of likeliness that's in some of the other case series.
I'm not sure what this article, which is one patient, adds, considering that it's published in a journal that I've never heard of from a somewhat disrupted -- disreputable pub -- Hindawi Press is notorious for -- I think they have something like 1,000 journals, and I'm often asked to be contributing articles to their journals that I'm not sure if they even exist. But I guess this must have existed, but it's not a very reputable place for this to have been published.
Q. Move to strike.
Taking the information described in this case report, assuming it to be accurate, as you described it, the improvement of the villous architecture, the resolution of the clinical symptoms of diarrhea, vomiting, and a 20-pound weight loss, when you put all that together with all the information provided here, the most likely cause for this syndrome is olmesartan; correct?

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MR. CHRISTIAN: Objection. Form.
THE WITNESS: I think as they laid it out here in this very low-tiered journal and a single patient, I'd be willing to say that with the way they presented the data that this is the most likely cause, but I really can't be sure --
BY MR. SLATER:
Q. Thank you.
A. -- of other potential factors in this case.
MR. SLATER: Move to strike from "but" forward.
Let's look at document 10 now, the Greywoode article.
THE REPORTER: Exhibit 16.
(Document marked for identification purposes as Gutman Exhibit 16.)
THE WITNESS: Oh, this is a different Greywoode, is it not? Oh.
BY MR. SLATER:
Q. Doctor, did you do any power

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calculation in connection with the number of patients studied in this article?
A. No.
Q. Of over -- rephrase.
Of over 2,000 patients in the endoscopy group, only 22 had been on olmesartan ;correct?
This is what it says on page 7 of your report at the top.
A. Okay. Okay.
Q. Did you evaluate whether 22 patients was enough in that group to come to a statistically significant conclusion one way or the other?
A. So one of the things that, you know, you can do is, you can look at confidence intervals and, you know, you can get some assessment by the -- by that what the confidence level you should have about the conclusions.
And, you know, the P value --
Q. They actually talk about that on page 1243 just above the conclusion; right?
A. Yeah, they --
Q. They actually evaluate the data

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and say because of the low number of patients taking olmesartan that there may be an association not detectable because of the power; right?

A. Yeah, I think that's fine. Sure. You can say that.

Yet, in the beginning of the paragraph, they say:

"The strength of the study includes the large sample size as well as the comprehensive and protocol direct in-person solicitation of medication use."

Q. That would be a large sample size of the total number of people studied --

A. Right.

Q. -- but when you look at the total number of people on olmesartan, that's a very low number; correct?

A. I mean, it's low. I don't know if I would say very low.

Q. 0.7 percent to 1 percent of the study participants, which was a total of 22 patients who got endoscopy and 83 out of over 12,000 who got colonoscopy.

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So it's a total of 105 patients; right?

A. Uh-huh. Right. But, for example, if you look at the -- the pathology reports section of the results in the abstract, when you look at a P value of .61 for what they're calling histologic diagnosis of celiac disease -- so we all agree that maybe that wasn't the best choice of words, but for histologic diagnosis of villous atrophy and inflammation.

So a P value of .61 suggests that you're so far away, you would probably need to increase the number of patients. Well, actually, here it's a little confusing the way it's written because they're combining endoscopy and colonoscopy.

But you would have to increase the number of patients by a massive amount to ever see any association. To the point because the P value is .6. It's so far away from ever being significant.

Q. And that analysis would apply basically across the board in terms of how many patients you'd need if you were going to run a

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study to try to see this type of association or causal association; correct?

A. I think it really depends. I cannot give you a generalization because the way all these types of studies were done are very different.

I mean, as you know, there's multiple studies from the same institution that were all done a completely different way. Because you have Greywoode, Lagana. And what's the other one? And DeGaetani.

So it's like, you know, they were -- they were all done in totally different ways. So I can't generalize between studies if that's what you want me to do.

Q. Did you read Dr. Lebwohl's deposition transcript?

A. I skimmed through it a long time ago. I don't remember the exact date.

Q. It's not on your list.

A. I don't think I spent more than about five minutes on it. We can add it to the list.

Q. And you didn't list Dr. Lagana's

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deposition transcript either, did you?

A. I don't remember reading his.

Q. I'm sorry. I didn't hear you. What?

A. I don't remember reading his.

MR. SLATER: Laura, let's go to document 3. I think it's document 3. It might be 3 or 21. It's a letter. "Olmesartan-induced enterocolitis" in "Pathology."

MS. PITTNER: Got it. It's 21.

MR. SLATER: Thanks.

THE REPORTER: Exhibit 17.

(Document marked for identification purposes as Gutman Exhibit 17.)

BY MR. SLATER:

Q. Doctor, looking at this, it's a letter written by Gallivan and Brown, and they talk about a 78-year-old woman. They give her clinical history, who had been prescribed olmesartan for four years.

Do you see that --

A. Yes.

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Q. -- in the left column?
A. Yes.
Q. It talks about her other regular medications and that there was no history of recent use of a nonsteroidal anti-inflammatory medication.
A. Right.
Q. And that over the past four months, she experienced severe watery diarrhea, which resulted in three hospital admissions, including intensive care unit admission for acute renal failure secondary to dehydration.
Do you see that?
A. Right.
Q. Then it says that upper endoscopy and colonoscopy were performed and the biopsies revealed mild villous blunting in the proximal small intestine with intraepithelial lymphocytosis and lamina propria inflammation; correct?
A. Yes.
Q. That's what's related there?
A. Right.
Q. They then talk about the

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colonoscopy and the findings on the colonic biopsies.
And then if you go into the second column, they talk about the fact that serum tissue transglutaminase antibodies were negative, and the clinical setting did not support an autoimmune enteropathy or immunodeficiency syndrome.
Do you see what I just read?
A. Yes.
Q. Then they say:
"Withdrawal of olmesartan and atorvastatin with implementation of total parenteral nutrition and oral budesonide produced resolution of diarrhea. On selectively recommencing only olmesartan and oral intake, the diarrhea returned."
Do you see that?
A. Yes.
Q. "Her anti-hypertensive medication was subsequently changed to ramipril and the diarrhea again resolved."
And then they talk about the fact that a subsequent colonoscopy was done and showed

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complete resolution of the enteropathy-like changes.
That's -- that's what is related in terms of the clinical course of that patient; correct?
A. Okay.
Q. The fact that when they discontinued the olmesartan and then put her back and it looks like in a controlled way, selectively recommencing only the olmesartan, the diarrhea returned.
That's what it says; right?
MR. CHRISTIAN: Objection. Form.
THE WITNESS: Well, an important point is that they also reinstituted oral intake. So the bowel rest that she had had where she was on TPN was no longer in play. So there could have been something related to the oral intake like that could be leading to the diarrhea as well.
BY MR. SLATER:
Q. Okay. It's more likely that when they took her off the olmesartan, she got better. Then they put her back on it.

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Even the fact that they let her have oral intake again, as between the two, the likelier cause of the diarrhea would be the olmesartan; correct?
MR. CHRISTIAN: Objection. Form.
THE WITNESS: Well, not if she had seronegative celiac disease and she went on oral intake that had gluten in it.
BY MR. SLATER:
Q. Let's look at what happened next.
Then they changed her anti-hypertensive to take her off olmesartan again and she got better again.
When you have -- so now we have a positive dechallenge, a positive rechallenge, and another positive dechallenge.
When you look at that together, for this patient with the information here, the most likely cause of her gastrointestinal syndrome is the olmesartan; correct?
MR. CHRISTIAN: Objection. Form.
THE WITNESS: You know, again, it's like the last case. Your -- your

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quality of evidence here, this is below a case series. It's just an individual case report.

So I don't dispute that on face value it looks like this is the most likely cause, but this is one patient, again, published in a journal that I've never heard of.

BY MR. SLATER:

Q. Based on the evidence here, the most likely cause is the olmesartan, just taking the evidence presented here; correct?

MR. CHRISTIAN: Objection. Form.

BY MR. SLATER:

Q. That's what you just said; right?

MR. CHRISTIAN: Same objection.

THE WITNESS: I mean, I think telling a story like a novel is -- doesn't really meet criteria for causation of a -- a global causation. This is just sort of like reading a story.

BY MR. SLATER:

Q. Move to strike.

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Very simply, and I think you just said it two answers ago.

Based on the information in this case report, for this patient the most likely cause of the gastrointestinal syndrome is the olmesartan; correct?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: With the information that's presented here, but I haven't had the opportunity to review this case record, to the extent that I have been able to with some of the cases in this litigation.

MR. SLATER: Move to strike from "but" forward.

Let's look now at document 12. Let's mark that.

THE REPORTER: Exhibit 18.

(Document marked for identification purposes as Gutman Exhibit 18.)

BY MR. SLATER:

Q. All right. Doctor, this article, which I believe is on your list, I want to go to

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the conclusion of this article written by Marietta, Cartee, Rishi, and Dr. Murray.

His conclusion -- his conclusion is:

"The drug-associated enteropathy that is most common and serious is that seen with olmesartan albeit at an extremely low rate."

You see what I just read?

A. Yes.

Q. Okay. Dr. Murray then states:

"One should then suspect OAE in any patient who presents with severe diarrhea and weight loss. Many of the features associated with OAE are also found in the enteropathy found in celiac disease. Because of this, one should review any celiac disease diagnosis for any use of olmesartan at the time of diagnosis."

A. Right.

Q. Do you see what I just read?

A. Yep.

Q. That's a reasonable recommendation to physicians what I just read from Dr. Murray; correct?

A. I mean, this is an opinion piece.

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So, you know, I don't have a way to put it in any context other than that.

Q. The question is: Is that a reasonable recommendation to physicians seeing patients with this type of a clinical presentation? Do you agree that's a reasonable recommendation?

A. I think that in medicine we always like to be conservative, and if we think that anything has been published, we always factor that into our consideration.

Q. If a patient comes into a gastroenterologist or a family physician, whoever it may be, who takes olmesartan and the patient has severe diarrhea, dehydration, and weight loss, based upon the medical literature as it stands now, it's a reasonable -- reasonable decision to take the patient off the olmesartan and see if the patient gets better, and if the patient does, to just switch their anti-hypertensive and avoid having to do invasive biopsies and that sort of thing.

That's a reasonable approach; correct?

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MR. CHRISTIAN: Objection. Form.
THE WITNESS: So I think the reasonable approach if somebody is that sick is to stop any medication that you can find that's ever been associated with a GI distress, and then make a decision about for each of those medications whether they're needed or not or whether an alternative can be used. So there's many medications that can cause GI side effects.
BY MR. SLATER:
Q. Let's -- let's talk about a patient who is on olmesartan and is not taking any other medications that cause severe diarrhea, dehydration, and weight loss, that that's -- olmesartan is the only drug they're taking that is known to cause that spectrum.
Based on the literature that exists now, if a patient came into a doctor reporting those symptoms, it would be reasonable for the doctor to stop the olmesartan and then, if the person were to improve and then get better, to not restart the olmesartan but to go

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to another high pressure -- high blood pressure medication; correct?
MR. CHRISTIAN: Objection. Form.
THE WITNESS: I think that's reasonable, but I don't think that most doctors are aware of this syndrome.
MR. SLATER: Let's take a break for about five or 10 minutes. I'm pretty close to being done, if not done. Let me just check my notes, all right, Randy? And then I think I might be done.
MR. CHRISTIAN: All right. Thanks, Adam.
THE VIDEOGRAPHER: Time is 3:27. We're going off the record.
MR. SLATER: Let's go off the video.
(A brief recess was taken.)
THE VIDEOGRAPHER: The time now is 3:42. We are back on the record.
BY MR. SLATER:
Q. Doctor, in looking at your report, you mentioned the Bradford Hill criteria, which we talked about earlier, and that you

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looked at that criteria based on the GRADE approach, Grading of Recommendations, Assessment, Development, and Evaluation approach?
A. Right.
Q. That approach, the GRADE approach, is that something you brought to this, or is that something that the attorneys asked you to use?
A. So I was asked to be sure to address the Bradford Hill criteria, and then I spent time on my own trying to find good articles that carefully described that nomenclature, and I found the two that I cited here. And I felt that the -- I saw multiple references to this GRADE approach and so I -- I tried to find what looked like an earlier original use of it, and that's how I found the article. So it was all something that I found.
Q. The GRADE approach, you had not applied that or used that previously; correct?
A. Correct.
Q. Did you actually apply the GRADE approach in terms of how you calculate the value of different criteria, or did you just generally,

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you know, consider it as you applied the Bradford Hill criteria?
A. I think I just generally considered it.
Q. Now, I just want to come back to one thing, and this is really the most important question of the day.
We talked about the Basson studies and some questions you had about the French data.
I just want to know: Is that because of your concern that the French have outrageous accents?
A. (Laugh). I told you. I've got two in my lab now and I had two other post-docs. So I've had four French people work with me. So that's not the problem.
Q. Okay. I just want to make sure that there's not a Monty Python issue here.
A. No.
Q. That's -- I want to reserve the rest of my time for requestioning if defense counsel questions Dr. Wilson. Thank you.
THE VIDEOGRAPHER: Randy, before

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we go, am I supposed to tape?
MR. CHRISTIAN: I just have a few questions, Adam. I'm fine with not switching the camera, but whatever you -- if you're fine with it, we can just do my questions without.
MR. SLATER: Whatever you want to do.
MR. CHRISTIAN: Yeah, let's just -- I don't look as good as Adam. So I'll stay off the camera.
MR. SLATER: (Laugh). Thank you. I'm really feeling flattered. (Laugh).
MR. CHRISTIAN: All right. Are you ready, Adam? We're still on the record?
THE VIDEOGRAPHER: Yes.
MR. CHRISTIAN: Okay.
EXAMINATION
BY MR. CHRISTIAN:
Q. Dr. Wilson, my name is Randy Christian. I represent the defendants in this case.
Do you understand that?

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A. Yes.
Q. Okay. I'm handing you what's been marked as Exhibit 9 to your deposition, which you indicated was your updated CV or resume, as of what date?
A. February 20, 2017.
Q. Okay. And is Exhibit 9, is that a true and correct copy of your CV?
A. Yes.
Q. Does it accurately summarize your education, training, and professional experience?
A. Yes.
Q. Will you turn to your report, which is Exhibit No. 4 in this case.
Do you have your report in front of you?
A. Yes.
Q. Turn to page 10. At the bottom of page 10, you were just asked a few questions about -- this is where the section starts on the Bradford Hill criteria; is that correct?
A. Yes.
Q. Okay. I want to ask you some questions about this criteria.

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The number one criteria you list there is strength of association; correct?
A. Correct.
Q. In your evaluation of general causation in this case, did you evaluate the strength of the association that you found in the published medical literature?
A. Yes.
Q. Is that something that you do every day in your practice and in your research is evaluate strength of association?
A. Yes, I --
MR. SLATER: Objection.
BY MR. CHRISTIAN:
Q. You can still answer.
A. Yes, I do that. Whenever I'm considering any type of data that's published, whether it be something that's already published or something that I'm handling as an editor for a journal or whether I'm handling as a reviewer for an article, I need to determine what I think the quality of the associations are within that work.
Q. And you use -- utilize that methodology in your evaluation in Exhibit No. 4,

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your report?
A. Yes.
MR. SLATER: Objection.
BY MR. CHRISTIAN:
Q. Or did you use that methodology in your report?
A. Yes.
Q. What is the second criteria listed on the top of page 11?
A. It should be consistency.
Q. Okay. And did you evaluate consistency in looking at the evidence in this case as it relates to olmesartan and sprue-like enteropathy?
A. Yes. In fact, that's really a striking flaw in the literature is that there is so much inconsistency in trying to define this syndrome, and I've discussed some of this in my deposition today.
Q. And in looking at the issue of consistency, is that something that you do every day in your practice and research?
A. Yes.
Q. The next item there listed is

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temporality or study design suitability; is that correct?
A. Yes.
Q. And did you use the methodology of analyzing temporality or study design suitability in coming up with your opinions in this case?
A. Yes.
Q. Is that something you do every day in your practice and research?
A. Yes. We often have --
MR. SLATER: Objection.
THE WITNESS: Can I continue?
BY MR. CHRISTIAN:
Q. Yes.
A. So often in designing our human studies -- for example, I'm mentoring a senior fellow, who's joining our faculty in a new study that we're starting, and we had to very carefully think through the study design of the measurements we were going to make in patients on and off the medication for Crohn's disease. And we do the same thing when we design animal experiments.

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Q. And the next item listed there is biological gradient.
Can you explain what that means?
A. So it's very important to consider the idea that if something just is cytotoxic at a low dose and you can't establish if there's a gradient, it's very hard to determine the effect in an experimental system.
In the human system, it's implicit that if somebody -- if patients were to have a deleterious effect of a medication, it seems that there should be some evidence of a dose effect; i.e. that, for example, some medications might be well tolerated at one dose, but if you increase it high enough, it could lower the seizure threshold and they could get seizures, or it could cause acute renal failure or what have you.
So that oftentimes it's very important to be able to determine if there is a gradient to an adverse effect.
Q. And, Dr. Wilson, did you analyze biological gradient in your analysis as summarized in Exhibit No. 4?

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A. Yes. In fact, I indicated that there's no evidence of a biological gradient in these studies.
Q. And is evaluating biological gradient something you do every day in your practice and research?
A. Yes. When we design experiments, we often will do a dose-response of an inhibitor. We will use dose-responses of a stimulant that we're using, such as the amount of bacteria we add to cells. So we're always factoring that type of thing in.
Q. And with respect to the next category listed, specificity, do you evaluate the issue of specificity as a methodology in your everyday practice?
A. Yes, it is.
MR. SLATER: Objection.
THE WITNESS: So there's this concept of whenever you're evaluating any clinical studies, you should factor in sensitivity and specificity, but in the, you know, that's sort of assessing, for example, the merits of a certain test.

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Here what we're looking at in specificity, it's something different. We're trying to see, to determine if there were to be causation, there needs to be a very specific outcome from a specific exposure.
So this idea that there could be a loose collection of responses is something that, in my opinion, lowers the quality of the evidence.
BY MR. CHRISTIAN:
Q. Did you utilize this methodology in coming up with your opinions in Exhibit No. 4?
A. I did.
Q. The next one is called biological plausibility.
What is that?
A. Well, I think that's the biggest sticking point in this entire case, which is that in order -- it's my understanding that, according to Bradford Hill criteria, in order for something to be likely to be causal, there should be a plausible biological mechanism.
And in this scenario, I gave the

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example of how things like the immunosuppressive effects of HIV can be quantified by looking at a CD4 count, for example, and that can be predictive of whether people get an immunocompromised state that leads to opportunistic infection.

Here we don't have any evidence of any particular driving force because it was originally speculated that it would be TGF beta driven, a loss of TGF beta immunoregulation, but that was really an overly simplistic thought process and there are many immunoregulatory pathways and, in fact, when they looked in the Marietta paper at TGF beta, signaling they couldn't see any differences.

Q. Dr. Wilson, was part of your methodology in coming up with your opinions in Exhibit 4 analyzing biologic plausibility?

A. It was.

Q. And is that something you do in your everyday practice and research?

A. Absolutely.

Q. Number 7 is coherence.

Did you analyze coherence in

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looking at the medical literature that you summarize in Exhibit No. 4?

A. So I found this one to be tough because that's supposed to be looking at the natural history of a disease, and since this is a syndrome that seems to occur in a very small number of cases, I found it very difficult to put together a coherent explanation of what this disease process is. So, for example, as I enumerated here, because of the poor quality of the evidence.

Does it include things like gastric and colonic involvement? Is that necessary to say that somebody has the syndrome? What is the role of the HLA status? What is the role of various other factors that were put forth but don't seem to be consistent between the studies?

So that further evidenced that causation is less likely because there's not coherence between the studies.

Q. As part of your methodology in coming up with your opinions in this case, did you utilize the concept of coherence?

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A. I tried to see if there was any, and I didn't find much evidence of that.

Q. Is that something that you do in your everyday practice and research?

A. Yes.

Q. Number 8 is experimental evidence.

Did you use in your methodology an analysis of experimental evidence relating to sprue-like enteropathy and olmesartan?

A. I tried, but I couldn't find much. The Marietta paper, I already discussed in my report that the deficiencies there in terms of trying to provide evidence of a mechanism, and also animal data is weak. So the experimental evidence is something I considered, but it's poor.

Q. Do you, Dr. Wilson, analyze experimental evidence in your everyday practice and research?

A. I do that a lot. That's what I do every day.

Q. Okay. And number 9, reasoning by analogy.

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Did you evaluate reasoning by analogy as part of your methodology in coming up with your opinions in this case?

MR. SLATER: Objection.

THE WITNESS: Yes, I did because I considered whether or not other ARBs could have the same effect, and the evidence on that is the jury is still out, so to speak, because there's a couple of scattered case reports, but there hasn't been any real effort to try and show that it's a class-specific effect. So there's not really any reasoning by analogy.

BY MR. CHRISTIAN:

Q. So in your everyday practice at Vanderbilt University and your work at the VA hospital, do you incorporate these nine different methodologies when you're trying to determine whether something is causing something else?

A. I do.

MR. SLATER: Objection.

MR. CHRISTIAN: Thank you, Dr. Wilson. That's all the questions I

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have.
MR. SLATER: I have a few follow-up questions.
FURTHER EXAMINATION
BY MR. SLATER:
Q. Start at the end and might just to be clear, you don't believe that any other ARBs cause sprue-like enteropathy or a similar syndrome? You don't believe that there's adequate evidence to make that statement.
Do I understand you correctly?
A. I didn't say that there's no evidence whatsoever. There's a few scattered case reports, and so I don't know whether anybody has really done anything more other than the articles I reviewed.
So, for example, in the Lagana study, they also looked at other ARBs, other ARBs, and didn't seem to find much of an association, but I don't know what other literature might come out in the next couple years.
Q. Do you have an opinion right now to a reasonable degree of medical certainty as to

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whether other ARBs cause a similar syndrome to sprue-like enteropathy or olmesartan-associated enteropathy?
A. I think from the few case reports, I wouldn't use the word "cause." I would say it is possible that there could be an association with some of the other ARBs, but right now the -- the clicker in terms of counting the number of cases is -- is still low.
Q. In your analysis of the Marietta article, which you were just asked about, you talked about CACO 2 cells. Remember you talked about a little of that in your report a little?
A. Yes. Yes.
Q. Yes?
A. Yes.
Q. And it's inappropriate to use CACO 2 cells in evaluating small intestinal mechanisms.
You're not saying that, are you?
A. So CACO 2s are a hotly debated cell model. So there are -- there are -- they are a poorly differentiated colon cancer cell line, and some that work with them have argued

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that you can manipulate them in culture to more closely mimic either colon or small intestinal cells. But they're not really a very good model of small intestinal cells because they're colon cancer cells.
Q. It is accepted in the scientific world that you can use CACO 2 cells to evaluate small intestinal disease processes; correct?
A. I think that's controversial. I don't think it's accepted.
Q. Studies in the peer-reviewed literature where CACO 2 cells were used, for example, to evaluate issues with celiac disease; correct?
A. There may be, but, again, it's just a cell culture model. You know, it's just one piece. It's just one model system.
Q. The fact that they used CACO 2 cells in the Marietta study, that's not a reason in and of itself to discount or invalidate those findings; correct?
A. I mean, if they had done the studies in a better manner where I would find the data more interpretable, you know, if it were to

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go into a better journal like "Gastroenterology," we would require that they provide evidence in a nontransformed system, such as a small intestinal aneroid, which are primary cell cultures, either 2- or 3-dimensional cultures.
Q. Okay. Move to strike.
The question I'm asking is very simple.
In your opinion, are you relying on the use of CACO 2 cells by the group in the Marietta study as a reason to reject their findings?
A. It's one of the reasons. It's not a -- it's not the only reason.
Q. Do you acknowledge that people studying celiac disease use CACO 2 cell cultures to experiment and study issues with celiac disease?
A. I would have to review that. I'm not certain about that, about how commonly that's done.
Q. Would you agree with me that the mechanisms described in the Marietta article could possibly be related to the mechanism

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whereby olmesartan causes this syndrome that's been identified with olmesartan?
MR. CHRISTIAN: Objection.
BY MR. SLATER:
Q. Do you agree that it's possible that regardless of the flaws that you identify in the study that the conclusion as to the mechanism is accurate?
MR. CHRISTIAN: Objection. Form.
THE WITNESS: I don't think that anything that they published in that article is valid.
BY MR. SLATER:
Q. Well, my question is this. You challenge many things about how the study was done and reported, but my question is this.
It's possible that the conclusion is correct despite those flaws that you identify; correct?
MR. CHRISTIAN: Objection. Form.
THE WITNESS: So the only thing that made it into the conclusion was something vague about immunopathogenesis, which is not -- doesn't say anything, and

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they relied on this idea of the IL-15 overexpression, but the data that was presented for that I did not consider to be valid.
I have a color version of that article. I don't know where it went.
BY MR. SLATER:
Q. Have you ever cited the Bradford Hill criteria in any paper you've ever published?
A. No.
Q. Have you ever taught students the use of the Bradford Hill criteria?
A. So I have not called it that, but in reviewing that for preparation of this, I realized that many of the principles, I have absolutely taught students and residents, post-docs, and junior faculty.
Q. Okay. Move to strike.
Have you ever in teaching students referred to the Bradford Hill criteria per se?
A. No.
Q. In writing any papers or teaching, have you ever referred to the GRADE

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approach, which you refer to in your report?
A. No.
Q. In any paper or anytime you've spoken to students, have you ever referred to the Oxford Centre for Evidence-Based Medicine standards that you refer to in your report?
A. No.
MR. SLATER: I have no other questions, unless counsel comes back again. Then we'll play tennis.
MR. CHRISTIAN: No questions. Thanks a lot.
THE VIDEOGRAPHER: Time now is 4:03. This deposition has concluded.

(Deposition concluded at 4:03 p.m.)

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ACKNOWLEDGMENT OF DEPONENT

I,_____, do hereby certify that I have read the foregoing pages, and that the same is a correct transcription of the answers given by me to the questions therein propounded, except for the corrections or changes in form or substance, if any, noted in the attached Errata Sheet.

_____

KEITH T. WILSON, M.D. DATE

Subscribed and sworn to before me this _____ day of _____, 20____.

My commission expires:_____

_____

Notary Public

CERTIFICATE OF REPORTER

DISTRICT OF COLUMBIA)

I, DENISE D. VICKERY, CRR/RMR and Notary Public, hereby certify the witness was by me first duly sworn to testify to the truth; that the foregoing deposition was taken at the time and place stated herein; and that the said deposition was recorded stenographically by me and thereafter reduced to printing under my direction; that said deposition is a true record of the testimony given by said witness.

I certify the inspection, reading and signing of said deposition were NOT waived by counsel for the respective parties and by the witness; and that I am not a relative or employee of any of the parties, or a relative or employee of either counsel, and I am in no way interested directly or indirectly in this action.

Denise D. Vickery, CRR/RMR

My Commission expires February 14, 2018

WORD INDEX